REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application and the indication that claims 15-18 are in a condition for allowance. Applicants request reconsideration of the subject application based on the following remarks.

Claims 14 was rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 14 has been amended to depend only from claim 12. No new matter has been introduced by virtue of these amendments.

Applicants believe that the claims as amended are fully compliant with the requirements of 35 U.S.C. §112 including the requirements of 35 U.S.C. §112, second paragraph.

Reconsideration and withdrawal of each of the §112 rejections are thus requested.

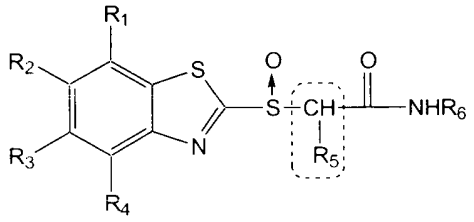
Claims 9-12 and 14 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Hirai et al. [JP 04139172].

The rejection is traversed.

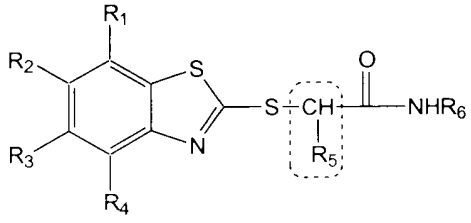
As in the prior rejection, the cited documents simply do not suggest the compounds recited in the pending claims, or the claimed methods of treatment.

The present compounds are structurally different from those disclosed in the cited prior art by the above amendments.

Hirai teaches compounds of the formula



and



Where R_5 is H, alkyl or aryl; and R_6 is Alkyl or aryl.

The compounds of Hirai are conformationally restricted in part because the benzoxazole group and the amide group are linked by a methylene or a 1,1-ethanediyl linker. The benzoxazole group and the amide group have a limited number of low energy conformations in part because the sterically crowded central carbon atom linking the two groups bears three substituents (i.e., the benzoxazole group, the amide group and the R_1 or R_5 group).

The compounds recited by Hirai comprise two atom linker between the benzoxazole group and the amide group, i.e., these groups are linked by a sulfur (or sulfoxide) and a methylene linker. The relative orientation of the benzoxazole group and the amide group is therefore limited by the limited degrees of freedom for rotation about the bonds linking the benzoxazole group, the sulfur atom, the methylene group and the amide group. Substitution of the methylene group, e.g., the methyl group of a 1,1-ethanediyl linker, further limits the available conformations of the molecules disclosed by Hirai in part because of steric interaction between the methyl group and at lease one of the benzoxazole group or the amide group.

In contrast, the present invention provides compounds of Formula I, IA and III where the linker between the benzoxazole residue and the N-heteroaryl amide (e.g., -C(O)NHAr) comprises at least a two (2) carbon diradical, e.g., a 1,2-ethylene or a α,ω-alkylene group. More

particularly, the alkylene linkage, $-(CH_2)_nCR_4R_5-$ has between 2 and 16 carbon atoms in the main chain linking the benzoxazole residue and the amide group of the compounds of Formula I or II. None of the compounds provided by the present invention have a methylene group, e.g., a $-CH_2-$ linkage between the benzoxazole residue and the N-heteroaryl amide (e.g., -C(O)NHAr).

Thus, the present invention provides compounds in which the benzoxazole group and the amide group are separated by a greater distance (at least two carbon atoms linked by single covalent bonds in between the benzoxazole group and the amide group) and the linking group of the compounds of Formula I and II provide greater conformational flexibility than the compounds of Hirai (two or more methylene groups, at least one of which has one non-hydrogen substituent can freely rotate such that the steric interaction between the benzoxazole group and the amide group is minimized).

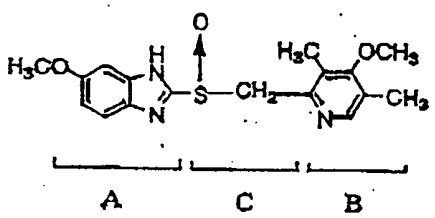
The importance of the linking group between the benzoxazole group and the amide group is further illustrated by a review of a structure-activity relationship (SAR) study conducted for Omeprazole and related compounds. The SAR study investigated the effect on varying the size and substitution pattern on a linker group C in Omeprazole, which is a H^+, K^+ ATPase inhibitior.

As the reference is understood, Hirai teaches compounds which possess gastric secretion inhibitory activity and antiulcer activity. Moreover, Hirai teaches that the disclosed compounds' efficacy results from H^+, K^+-ATPase inhibition.

A structure-activity relationship (SAR) study on the H^+, K^+-ATPase inhibition activity has been conducted for Omeprazole, which is a compound having a similar structure to those compounds recited by Hirai. See, A. Brandstrom, et al., *Scand. J. Gasteroenterol.*, 20, (Suppl. 108), 15-22 (1985), a copy of which is enclosed for consideration by the Examiner. The structure of

Omeprazole is divided into three structural elements, i.e., (A) benzimidazole ring, (B) pyridine ring and (C) the chain linking elements (A) and (B).

Omeprazole

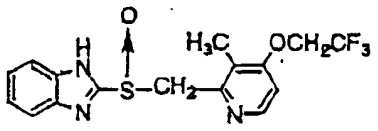


The Brandstrom publication discloses in vivo physiological activity for a series of compounds in which the (C) element of Omeprazole is varied. More particularly a series of compounds were prepared and tested in which the $-S(O)CH_2-$ (C) element of Omeprazole was replaced with $-SCH_2CH_2-$, $-SCH(CH_3)-$, $-SCH_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$. Only three compounds exhibited gastric secretion inhibition activity, e.g., those compounds in which the (C) element was a SCH_2-, $-S(O)CH_2-$, or $-S(O)CH(CH_3)-$ group. In contrast, the compound which had a $-SCH_2CH_2-$ (C) element (i.e., two carbon chains are adjacent to a sulfur atom) did not exhibit the gastric secretion inhibition activity. Thus, Brandstrom concluded that for Omeprazole derivatives to have gastric secretion inhibition activity *in vivo* the (C) element must comprise a -S(O)C- group (page 16, under the right column, 6-4 lines from the bottom of the page).

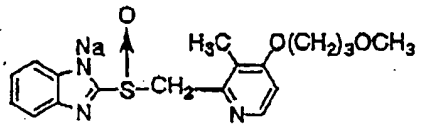
Brandstrom further recites that compounds comprising a $-S(O)CH(CH_3)-$ (C) element exhibited gastric secretion inhibitory activity in vivo where in contrast whereas $-SCH(CH_3)-$ group did not exhibit the inhibitory. The reason is argued that a sulfur atom was not oxidized in vivo due to the presence of methyl group (page 16, under the right column, 10-7 lines from the bottom of the page).

Brandstrom recites that Omeprazole variants must comprise a (C) element consisting of a single carbon atom and a sulfur atom in order to exhibit H^+, K^+-ATPase inhibition activity. The publication discloses a range of structural variation at the (C) element which illustrates the extremely restrictive structural tolerance at the (C) element for the compounds to have H^+, K^+-

ATPase inhibition activity. Other compounds possessing H^+, K^+-ATPase inhibition activity support the structural restrictions presented by Brandstrom's SAR study of Omeprazole. Lansoprazole, Sodium rabeprazole are ATPase-inhibitors in which the (C) element consists of a sulfoxide and a methylene group.



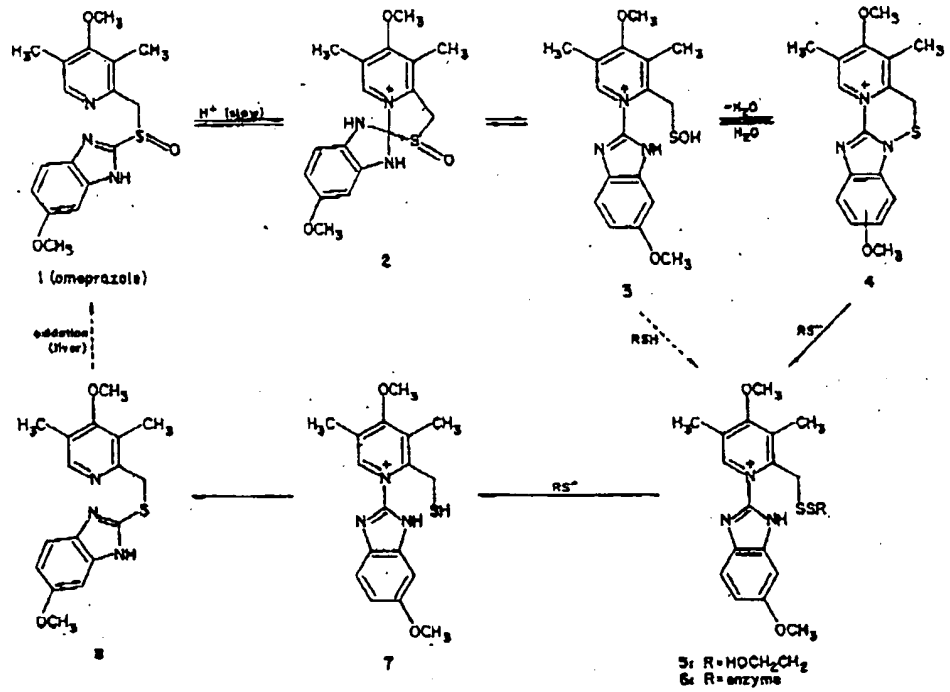
Lansoprazole



Sodium rabeprazole

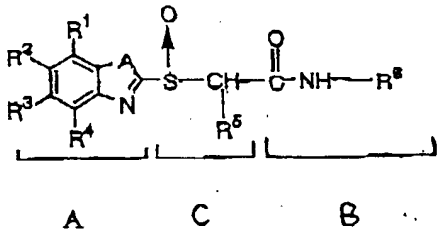
In another SAR study, Lindberg investigated the reaction mechanism *in vivo* for omeprazole type compounds. See, P. Lindberg, et al., *J. Med. Chem.*, 29(8), 1327-1329 (1986). More particularly, Lindberg recites that Omeprazole undergoes reversible cyclization by reaction of the sulfone sulfur with a nitrogen of the benzimidazole ring. The reaction mechanism to active compounds are suggested as follows.

Scheme I



In the scheme I, R represents enzyme, and therefore the compounds directly reacting with the enzyme are pyridinium compounds (3) or (4). An easily-cyclized 6-membered ring must be formed so that the pyridinium compounds (3) maintain equilibrant with the compound (4). For that purpose, the carbon chain of the above-mentioned (C) element must have only one carbon atom. Therefore, also in view of the study of the above reaction mechanism, it is desirable that the (C) element has only one carbon atom to form an easily-cyclized 6-membered ring.

The utility of the compounds disclosed by Hirai et al. (JP 04-139172) is H^+, K^+-ATPase inhibitor which reacts to the same enzyme as that of Omeprazole and has a similar .structure to Omeprazole. The structure of the. compounds of Hirai et al. is divided into the following three portions corresponding to the above-mentioned Omeprazole.

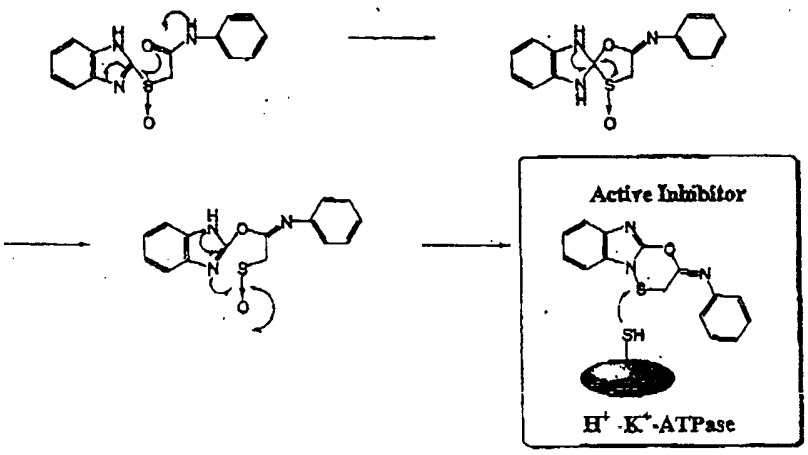


(A) portion represents benzazole in place of benzimidazole, (B) portion represents N-substituted amide group and (C) represents the carbon chain having one carbon atom.

It is described in the reference of Brandstrom et al. that (B) portion must be 2-pyridiyl group (page 16, under the right column, 4-2 lines from the bottom of the page), and it is clear from the study of reaction mechanism by P. Lindberg et al. that a nitrogen atom is required at the 2-position from the position bound to (C) portion. In the compounds of Hirai, an amide group of (B) portion corresponds to 2-pylidyle group of Omeprazole. The structure of the compounds is designed so that a nitrogen atom is located at the 2-position from the position bound to (C) portion, which is similar to the pyridine ring of Omeprazole.

The compounds of Hirai et al. are possible to have a similar reaction mechanism to

Omeprazole and the formula showing the structure is as follows.



The active compounds reacting with enzyme has a 6-membered ring which is similar to pyridinium compounds (4) described in the reference of P. Lindberg et al..

As above mentioned, the structure of the compounds of Hirai et al. can be divided into three portions of (A), (B) and (C) . The carbon chain adjacent to a sulfur atom in (C) must have only one carbon group, which is similar to Omeorazole in the reference of Brandstrom. Such features that the compounds have easily-cyclized 6-membered ring structure are evident from the teachings of the Lindberg document. Thus one skilled in the art would not have been motivated to increase the length of the carbon linker in the (C) element in part because the above process would be disfavored due to a seven menbered ring transition state.

The compounds of Hirai et al. are unable to exhibit H^+, K^+-ATPase inhibitory activity if the carbon chain has more than one carbon atom in (C) portion. in the reference of Hirai et al., the carbon atom adjacent to a sulfur atom may be substituted, but the carbon chain has only one carbon atom. It is not taught that the structure has more than one carbon atoms such as ethylene group.

Replacement of the methylene or 1,1-ethandiyl linker of the (C) element in omeprazole or by analogy the (C) element of the compounds recited by Hirai or Förster would create an unfavorable seven membered transient species in the *in vivo* reaction profile presented in Scheme I. Thus one skilled in the art, intent on developing new compounds having gastric secretion inhibition activity would not have been motivated to increase the length of the (C) element linker of the compounds disclosed therein.

From the above-described documents, it is quite evident that H^+, K^+-ATPase inhibitor may have the structure wherein (C) portion represents a methylene group or a substituted methylene group (i.e., a 1,1-ethanediyl group). In contrast, the above-described documents teach that incorporation of a (C) element having two carbons and a sulfur atom linking the (A) element (e.g., benzimidazole) and the (B) element (amide or pyridine ring) results in compounds which do not exhibit gastric secretion inhibition activity. Thus, one skilled in the art would not have been motivated to increase the separation of the benzimidazole ring and the amide group in the compounds recited by Hirai by incorporating an ethylene linkage in the (C) element.

The claims are therefore patentable over the art cited by the office action taken alone or in combination for at least the reasons discussed herein. Applicants request withdrawal of the rejections and reconsideration.

Although it is not believed that any additional fees are needed to consider this submission, the Examiner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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John B. Alexander (Reg. No. 48,399)
EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman
Intellectual Property Practice Group
P. O. Box 9169
Boston, MA 02209
Tel: (617) 439-4444
Fax: (617) 439-4170 / 7748